RFA CA-00-001
INTERDISCIPLINARY RESEARCH TEAMS FOR MOLECULAR TARGET ASSESSMENT
Special instructions for preparation of this U54 application

Special supplemental application instructions: Information on how to organize this grant and page limits for various sections

Applications are submitted on Grant Application Form PHS-398. This is available at http://www.nih.gov.grants/funding/phs398/forms_toc.html All information requested in the instruction booklet should be provided. In addition, the application should be responsive to the information requested below.

Form AA. FACE PAGE

Complete all items on the face page of the application. This is page 1 of the application; number succeeding pages consecutively.

In Item number 2, enter the appropriate title, INTERDISCIPLINARY RESEARCH TEAMS FOR MOLECULAR TARGET ASSESSMENT, and RFA number(CA-00-001), and check the YES box.

Form BB. DESCRIPTION, PERFORMANCE SITES, AND KEY PERSONNEL

On page 2, describe briefly the composite research program indicating the emphasis of the research projects. State concisely the overall goals of the entire grant and clearly state the contribution of each component to the overall theme and goals. Under Performance Sites, list the applicant institution and all other sites where work described in the research plan will be conducted. Key personnel for the entire program project, including consultants and consortium collaborators, if any, should be listed alphabetically. To aid in the review of the application, include information concerning the distribution of effort of key personnel on each project and core. This may be presented in tabular form (see Appendix B for example). Use additional pages only if needed to list personnel and performance sites.

Form CC. TABLE OF CONTENTS

The application is reviewed as a whole as well as project by project; therefore, prepare a detailed table of contents that enables reviewers to find specific information readily. Identify each research project and each core unit by title. Assign each research project a roman numeral (I,II,III) and assign each core unit a capital letter (A,B,C) that reflects the order in which the research projects and core units are presented in the application. A sample Table of Contents (Appendix A) is included at the end of these Guidelines as an example of how the order and format of the application could be organized.

Form DD. BUDGET ESTIMATES

Prepare a series of composite budget tables for the U54 grant as requested below. A detailed budget is also required for each Research project and core unit. The latter need not be repeated elsewhere in the application.

A. Composite Budget

Use page 4, "DETAILED BUDGET FOR FIRST 12-MONTH BUDGET PERIOD," of Form PHS-398 to present the total budget for all requested support for the first year. For each category, such as "PERSONNEL," "EQUIPMENT," etc., give only the aggregate amount requested for each research project and each core unit with subtotals.

If consortium arrangements involving other institutions or organizations are anticipated, include total (direct and indirect) costs associated with such third-party participation in the "CONSORTIUM/CONTRACTUAL COST" category. Costs for purchased services should be itemized under the "OTHER EXPENSES" category.

Use page 5, "BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD," of Form PHS-398 to prepare a budget, by category, that provides totals for each year of requested support. Requests for any increases in succeeding years must also be justified in the individual research project and core unit budgets (see below).

B. Individual Research Project and Core Unit Budgets (*)

1) First year (use page 4 of the PHS 398 for each)

2) Total project period years 02-05 (use page 5 of the PHS 398 for each)

Budget Justifications & Explanations: Describe and justify the personnel effort of all key personnel, consultants, collaborators, and support staff. Provide justifications for costs associated with laboratory and clinical research, animal research, equipment, equipment maintenance, imaging facilities and pathology. Travel funds should be requested for the Principal Investigator to attend the Planning Committee meeting in Washington, D.C. twice a year and for the Project Leaders to attend the Annual Meeting in Washington, D. C. once a year. If the grant application involves a consortium of institutions, funds should be requested for teleconferencing, videoconferencing and face-to-face conferencing as needed.

For all years, explain and justify any unusual items such as major equipment or alterations and renovations. For additional years of support requested, justify any significant changes in any category over the first 12-month budget period. Identify significant increases with asterisks against the appropriate amounts and provide justifications for these increases. If a recurring annual increase in personnel or other costs is anticipated, give the percentage; however, current

NIH practice limits escalation to 3 percent.

* Consortium budget (if applicable) same as B. Total direct and Facilities and Administrative (F&A) costs of sub-awardee to be shown under Consortium/Contract costs in the individual component budget and a detailed sub-awardee budget to be placed behind project/core budget.

Form FF. BIOGRAPHICAL SKETCH

Biographical sketches are required for all professional and key personnel participating in the research projects and core units (i.e., personnel listed on page 2). Begin with principal investigator/program director, and in alphabetical order thereafter, submit biographical sketches as directed in the "Instruction Sheet" for Form PHS-398. Do not exceed two pages for each person. Biographical sketches are required for all professional personnel participating in individual projects and cores and for all consultants. Do not repeat biographical sketches in each project or core. Include all biographical sketches in the application, not in an appendix.

Form GG. COMPOSITE SUMMARY OF OTHER SUPPORT

Information should be provided for each participating investigator following the sample format shown on Form GG. Comment on the extent of financial and/or scientific overlap of any of these grants or contracts with the proposed program project, how time and effort would be redistributed and what support would be relinquished if the program project were awarded.

Form HH. RESOURCES AND ENVIRONMENT

Complete the "Resources and Environment" page of PHS-398 for the overall project. Briefly describe the features of the institutional environment that are or would be relevant to the effective implementation of the proposed grant. As appropriate, describe available resources, such as clinical and laboratory facilities, imaging facilities, participating and affiliated units, laboratory models, patient populations, geographical distribution of space and personnel, and consultative resources. Please describe any relevant funded resources that would be utilized by this grant, such as Small Animal Imaging Facilities

RESEARCH PLAN

A. INTRODUCTORY OVERVIEW

This narrative should explicitly provide the required information in the order noted below: Utilize up to 20 pages for this section, including items 1-4 below.

1. Goals: Present the general target area(s) to be studied, the overall long-term objectives of the

research described in this application and any hypotheses to be tested.

2. Integration: A Team is a confederation of interrelated research projects and pilot projects. Address the issue of the integration of components, demonstrating how each individual component contributes to the overall Team. A diagram illustrating the effective interactions between components may be helpful to reviewers.
3. Research Plan: This section delineates the research addressed by the program as a whole and explains the strategic approach to the problem, briefly mentioning each research project or core as it relates to the overall Team.

Describe a (five year) research plan that demonstrates knowledge, ingenuity, practicality, and commitment in organizing a multiproject research team for conducting basic and clinical research. Describe why the target or pathway that you have selected is a high priority in the treatment or prevention of cancer. Describe the overall specific aims in terms of translating the basic biologic understanding of the target into assays and probes that can be used to assess the effect of agents on this target. Describe the process for choosing agents to evaluate the assays and probes . Describe the overall process for selecting assays and probes to develop (see below). Describe plans to assess the assays' and probes' feasibility and possible predictive value and to correlate the research tools with useful preventive or therapeutic activity. Describe the team members' experience with this target and agents directed at the target and with research tools such as assays, tools, reporter cassettes, molecular and cellular imaging, probes, etc.

Describe any prior collaborative efforts among investigators in the group.

4. Preliminary Studies: This section should focus on research already underway and current accomplishments of the investigators relevant to this research. More detailed preliminary reports are included separately under each individual project. Items to be included are:

o A summary of major accomplishments of the participating investigators that relate to the overall theme of the program project.
o A list of any relevant publications and manuscripts accepted for publication already produced by the interaction(s) of the participating investigators.

5. Organization and Administrative Structure: (3 pages) Describe the organizational framework including the chain of authority for decision making and administration, beginning at the level of the principal investigator. Include investigators responsible for individual research projects (project leaders) and how the projects are planned, coordinated, and evaluated. Provide information on plans for scheduled meetings to exchange information and data between clinical and basic investigators and review of progress. Include information on all ongoing activities or collaborations among the project investigators. Describe relationships between the Team and other funded relevant projects and the administrative functions of the Team.

Describe plans to establish any external and/or internal advisory committees and provide an

organizational chart. Applicants should describe a mechanism for reprogramming resources and revising team membership as needed to provide flexibility in addressing novel targets, such as an Team Oversight Committee and/or Pilot Project Review Committee. A Team should allocate significant effort to Pilot Projects that explore novel approaches. The applicant should propose an institutional review process that selects pilot projects which are innovative and likely to have impact on the evaluation of molecular effects of novel agents.

Assurances and Collaborative Agreements (length as needed). Any arrangements for collaborative endeavors or subcontracting should be described. Provide copies of all letters pertaining to consortium agreements and consultancies.

Patent Coverage. Since the discovery of new and improved research tools for the evaluation of anticancer treatments is the objective of this effort and active involvement by industrial laboratories is facilitated by the existence of adequate patent coverage, it is essential that applicants provide plans to assure such coverage. The situation could be complicated since multiple institutions are likely to be involved. Each Team must therefore provide a detailed description of the approach to be used for obtaining patent coverage and for licensing where appropriate, in particular where the invention may involve investigators from more than one institution. Procedures must be described for resolution of legal problems should they arise. Your attention is drawn to P.L. 96-517 as amended by P.L.98-620 and 37 CFR Part 401. Instructions were also published in the NIH GUIDE FOR GRANTS AND CONTRACTS, Vol.19, No. 23, June 22, 1990.

All Awardees must adhere to the policy for distribution of unique research resources produced with NIH funding, published in the NIH Guide for Grants and Contracts (NIH Guide, Vol. 25, No. 23, July 12, 1996). The Guide can be accessed electronically at http://www.nih.gov/grants/guide/index.html. Procedures must be described which address how Awardees will approach such distribution, including acknowledgment of the terms of any related technology licenses or sponsored research agreements which Institution may have.

NCI acknowledges that some commercial collaborators that are members of applicant Teams, or who provide agents to applicant Teams, may require that Institution agree to grant to them certain intellectual property rights, as described by the terms below. If Institution voluntarily agrees to the described terms, then they should appear in the Institution's Team proposal. NCI recognizes that Institutions' ability to access agents from commercial collaborators for this effort may be limited absent such a voluntary agreement, or a substantially similar independent agreement between Institution and commercial collaborators providing agents. However, in no event will the award of a cooperative agreement be dependent upon the described terms being part of Institution's Team proposal. Rather, Institution's Team proposal may provide Institution's own plan for accessing agents from commercial collaborators. In no event, however, will an award be made absent incorporation of either the terms below, or Institution's own plan.

"Institution agrees to grant to commercial collaborator: (i) a paid-up nonexclusive,

nontransferable, royalty-free, world-wide license to all Institution Inventions for research purposes only; and (ii) a time-limited first option to negotiate an exclusive, world-wide royalty-bearing license for all commercial purposes, including the right to sub-license, to all Institution Inventions on terms to be negotiated in good faith by the collaborator and Institution. The collaborator shall notify Institution, in writing, of its interest in obtaining such an exclusive license to any Institution Invention within six (6) months of the collaborator's receipt of notice of such Institution Invention(s). In the event that a collaborator fails to so notify Institution, or elects not to obtain an exclusive license, then the collaborator's option shall expire with respect to that Institution Invention, and Institution will be free to dispose of its interests in such Institution Invention in accordance with Institution's policies. If Institution and collaborator fail to reach agreement within ninety (90) days, (or such additional period as collaborator and Institution may agree) on the terms for an exclusive license for a particular Institution Invention, then for a period of six (6) months thereafter Institution shall not offer to license the Institution Invention to any third party on materially better terms than those last offered to collaborator without first offering such terms to collaborator, in which case collaborator shall have a period of thirty (30) days in which to accept or reject the offer.

Institution agrees that notwithstanding anything contained herein to the contrary, any inventions, discoveries or innovations, whether patentable or not, which are not Subject Inventions as defined in 35 USC 201(e), arising out of any unauthorized use of the collaborator's agent and/or any modifications to the agent, shall be the property of the collaborator (hereinafter "Collaborator Inventions"). Institution will promptly notify the collaborator in writing of any such Collaborator Inventions and, at collaborator's request and expense, Institution will cause to be assigned to collaborator all right, title and interest in and to any such collaborator inventions and provide collaborator with assignment or other documents). Institution may also be conducting other research using the agent under the authority of a separate Material Transfer Agreement (MTA) with the collaborator. Inventions arising thereunder shall be subject to the terms of the MTA, and not to this clause."

* 35 USC
(E) The term "Subject Invention" means any invention of the investigators first conceived or first actually reduced to practice in the performance of work under a funding agreement. . . ."

6. Literature cited: List complete literature citations at the end of the program narrative. Each should include names of all authors, full title, name of book or journal, volume, pages and year of publication.

B. RESEARCH PROJECT DESCRIPTIONS

For each research project, a full description of the project is to be provided following the format presented in Form PHS-398. A minimum of three Research projects should be included.

1. Title Page (PHS 398 Continuation Page; NOT page AA, FACE PAGE). Clearly denote the

project number, the title of the project and project leader.

2. Description/List of Key Personnel (PHS 398 Form Page 2-BB). The title of "Principal Investigator" is reserved for the director of the overall application. The directors of individual projects should be referred to as "project leaders" and directors of cores should be referred to as "core directors."

3. Do not repeat Table of Contents.

4. Do not repeat Budgets. All information should have been provided in previous budget description (Budget Estimates, B. Individual Research project and Core Unit Budgets).

5. Do not repeat Biographical Sketches and Other Support because these are included earlier in the application.

6. Resources (PHS 398 Form Page HH). Follow instructions on the form. List only those specific to the individual projects.

7. Research Plan

a. Project Aspects - Include Sections a-d (Instructions for PHS 398, Pages 1-17). Limited to 20 pages for each Research Project and 5 pages for each Pilot Project (see below). Describe the research plan for developing and assessing assays and probes as individual Research Projects with Pilot Projects. Thus, a tissue immunohistochemistry research project might be described that will develop new reagents to assess a change in the expression of a particular enzyme. How this technique would be used for the specific target and agents selected may be described as a separate Pilot Project in the Team. Describe possible limitations and pitfalls and how these might be addressed. The description of the research methodologies should include the appropriate negative and positive controls (e.g. the possibility of in vivo models for which you might expect a selected agent not to affect the target (if the target is mutated RAS, a model with wt RAS) and the agent has neither target effect nor antitumor effect). Describe plans to demonstrate the feasibility of the assays and probes and their possible predictive value and to correlate the probes with useful preventive or therapeutic activity in the appropriate models. Describe plans for defining the operating characteristics and quality control procedures for the probe and plans for its validation.

Research projects might include projects such as molecular, cellular and/or biochemical pharmacology of a particular pathway, immunohistochemistry approaches to enzyme alterations, radiochemistry to produce specific imaging agents, or others as the investigators determine are needed for this research plan. Although it is anticipated that a research project would be funded for the entire funding period, these grants are intended to provide flexibility to redirect resources in novel directions if the PI and designated advisory bodies determine that an existing project is not making headway, and that a novel project within the workscope should be substituted.

b. Program Aspects - (This item is NOT included in Instructions for PHS 398.) Describe in this section the relevance of the project to the primary theme of the Team's program and the collaborations with investigators within the Team. Describe interactions with other Research Projects and Pilot Projects and the contribution this project will make to accomplishing the goals of the Team. Limited to one page.

8. Gender, Children, and Minority Inclusion (Instructions for PHS 398, Pages 16, 17). Each project or core involving Human Subjects as described in the Instructions must include information in tabular form as shown in Appendix D. A table for gender and minority inclusion must be prepared for each clinical study in a project. Inclusion of children in the research studies must be addressed. Exclusion of children from the clinical trial may be justified by citing one of the following:
Exclusion 1 - The topic to be studies is irrelevant to children.
Exclusion 4b - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network.
See Human Subjects (pg. 27-32 for more information).

9. Human Subjects (Instructions for PHS 398, Pages 17-18, Item e). Applicants must provide clear evidence of full protection and monitoring of human subjects.

10. Vertebrate Animals (Instructions for PHS 398, Page 18, Item f). Self-explanatory.

11. Literature Cited (PHS 398 Continuation Pages; Instructions for PHS 398, Pages 18-19). List complete literature citations at the end of each project. Each citation must include the names of all authors, full title, name of book or journal, volume, pages and year of publication.

12. Consortium/Contractual Arrangements (PHS 398 Continuation Pages; Instructions for PHS 398, Page 19, Item h). Statement of intent to collaborate must be included

13. Consultants (PHS 398 Continuation Pages; Instructions for PHS 398, Page 19, Item I). List consultants specific to this project but external to the Interdisciplinary Research Team. For each consultant, include a letter of support detailing the nature and extent of participation.

C. DEVELOPMENTAL/ PILOT PROJECTS

For each Pilot Project, a full description of the project is to be provided following the format described above for Research projects except that the Research Plan is limited to five pages for each Pilot Project. The Pilot Projects should be designed to expand the basic understanding of the target pathway, create probes or assays or test their capability to measure drug effects on specific targets in proof-of-principle laboratory models and clinical trials. If a clinical trial is not described as one of the research projects, at least one Pilot Project should outline the general plan for a (future) clinical trial that incorporates the assays, probes, and techniques developed in the

Research Projects and a novel agent. Since the actual agents and research tools may not yet be available, the agent may be a hypothetical agent. Although the pace of this research is difficult to predict, it is expected that initiation of a proof of principle clinical trial would be feasible within the first three years. This clinical pilot project description should allow reviewers to assess the investigators' general approach toward evaluation of novel research tools in a clinical trial with a novel agent.

Time lines should be provided for each of the Pilot Projects. No more than two years can be requested for each Pilot Project. It is expected that funds would be reprogrammed for other Pilot Projects through the life of the cooperative agreement.

Applications from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research, if appropriate. If so, a letter of agreement from either the GCRC program director or principal investigator should be included with the application. Early clinical trials should be conducted in accordance with the instructions in the Investigators Handbook (URL: http:// ctep.info.nih.gov), or the DCP Clinical Trial Guidelines and Reporting Requirements, which describe the procedures and requirements for protocol development and submission, ordering investigational drugs from NCI, accountability and storage of investigational drugs, reporting of clinical trials results and adverse events and monitoring and quality assurance procedures.

D. CORE DESCRIPTIONS

1. Introduction

The cores of a U54 cooperative agreement may include laboratory and clinical facilities, equipment, and services which will be shared by multiple projects and/or pilot projects of the cooperative agreement. Each Core must support at least two Research projects and/or pilot projects. Discuss the overall objectives of the core units; present the organizational framework or chart; highlight the decision-making process for use of core unit services, plans for quality control, and identify the proposed core units by title. To aid in the review of your application, the proposed quantitative distribution of core usage may be indicated in a composite tabular form (see Sample Format - Appendix C). Do not exceed five pages for a core unit description

2. Administrative Core Unit

The Administrative Core may include support for administration, such as the costs of fiscal and business management, consultant, secretarial and clinical services associated with the cooperative agreement unless these items are included in the institution's indirect cost rate. Provide a description of arrangements for internal quality control of research, the allocation of funds, day-to-day management, contractual agreements, if applicable, and internal communication among investigators. Provide a description of all advisory committees including

external committees and internal decision making committees such as the Team Oversight Committee and Pilot Project Review Committee.
a. Objective;
b.Organizational Chart (if appropriate);
c. Staffing (Professional and Support);
d. Resources & Environment: provide description of space and physical resources;
e. Services Provided (current and projected use): describe services to other core units and research projects.

3. Technical Service Core Units
a. Objective;
b. Staffing (Professional and Support);
c. Resources & Environment;
d. Administration; include description of a charge back system and priority management procedures if the core will be configured in an open access format.
e. Justification: describe services provided with their bearing on productivity and quality;
f. Use: indicate estimated needs for usage (e.g., assays performed, animals supplied, etc.).

Form II. CHECKLIST for overall application (Use Form Page II; Instructions for PHS 398, Pages 19-20). Self-explanatory.

APPENDIX A: TABLE OF CONTENTS (SAMPLE)

SECTION I

Face Page
Table of Contents
Detailed Cooperative agreement Budget for First 12-Month Period
Budget Estimate for Each Year of Cooperative agreement
Summary of All Other Sources of Support
Biographical Sketches

SECTION II

Overall Research Plan for the Team
- Goals
- Integration
- Research Plan
- Preliminary Studies
- Institutional Environment and Resources
- Organization and Administrative Structure
- Literature Cited with complete titles and authors

Individual Research Project I (Title, Project leader)
- Title Page
- Resources and Environment
- Research Plan
- Preliminary Studies
- (Gender and Minority Inclusion)
- (Human Subjects)
- (Vertebrate Animals)
- Literature Cited with complete titles and authors
- (Consortium/Contractual Arrangements)
- Consultants/Collaborators

Individual Research Project II (Title, Project Leader)
- Title Page
- Description of Research Plan/Key Personnel
- Etc.

Pilot Project 1 (Title, Project Leader)
- Title Page
- Description of Research Plan/Key Personnel
- Etc.

Administrative Core A(Title, Core Director)
- Cover Page
- Description of Core
- Role and Justification for the Core Component
- Etc.

Core Component B (Title, Core Director)
- Cover Page
- Description of Core
- Etc.

Checklist

Appendix materials: Follow PHS 398 instructions.

APPENDIX B -
TABLE OF DISTRIBUTION OF PROFESSIONAL EFFORT (%) ON THIS APPLICATION (SAMPLE)

Participating Investigator	Core A	Core B	Project I	Project II	Project III	Application Total
Dr. A. (Principal Investigator)	10*	--	25*	--	15	50
Dr. B.	--	10*	--	--	--	10
Dr. C.	--	--	--	25*	10	35
Dr. D.	--	--	--	--	20	20
Dr. E.	--	--	30	--	30	60
Dr. F.	--	30	--	--	--	30
Dr. G.	--	--	--	25	--	25
Dr. H.	--	--	25	--	--	25
Dr. I.	--	--	--	--	50	50
--	--	--	--	--	--	--

*Project Leader/Core LeaderFirst lines should be reserved for project and core leaders; other investigators should follow thereafter.

APPENDIX C:
TABLE OF PERCENTAGE DISTRIBUTION OF SCIENTIFIC CORERESEARCH RESOURCES TO PROJECTS (SAMPLE)

Project	Project I	Project II	Project III	Total (100%)
Core A: Monoclonal Antibodies	60	--	40	100
Core B: Animal Maintenance	50	25	25	100
Core C: Administration	30	30	40	100

APPENDIX D:

TABLE OF GENDER AND MINORITY INCLUSION (SAMPLE **)**

Project/Study Title: Xxxxx Xxxx X Xxx

	American Indian or Alaskan Native	**Asian or Pacific Islander**	**Black, not of Hispanic Origin**	**Hispanic**	**White, not of Hispanic Origin**	**Other or Unknown**	**Total**
Female	0	7	10	2	15	--	34
Male	1	3	6	2	9	--	21
GenderUnknown	--	--	--	--	--	3	3
Total	1	10	16	4	24	3	85